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PSYCHOPATHOLOGY IN THE POSTGENOMIC ERA

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■ **Abstract** We are rapidly approaching the postgenomic era in which we will know all of the 3 billion DNA bases in the human genome sequence and all of the variations in the genome sequence that are ultimately responsible for genetic influence on behavior. These ongoing advances and new techniques will make it easier to identify genes associated with psychopathology. Progress in identifying such genes has been slower than some experts expected, probably because many genes are involved for each phenotype, which means the effect of any one gene is small. Nonetheless, replicated linkages and associations are being found, for example, for dementia, reading disability, and hyperactivity. The future of genetic research lies in finding out how genes work (functional genomics). It is important for the future of psychology that pathways between genes and behavior be examined at the top-down psychological level of analysis (behavioral genomics), as well as at the bottom-up molecular biological level of cells or the neuroscience level of the brain. DNA will revolutionize psychological research and treatment during the coming decades.

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INTRODUCTION

Psychopathology is the primary psychological target for molecular genetic attempts to identify genes. Most of what is known about the genetics of psychopathology comes from quantitative genetic research involving family, twin, and adoption studies, not just in demonstrating the ubiquitous influence of genes but also in going beyond heritability to investigate the genetic and environmental etiologies of heterogeneity and comorbidity, to understand the etiological links between the normal and abnormal and to explore the interplay between nature and nurture in development (Plomin et al. 2001a). This review, however, focuses on attempts to identify genes responsible for the heritability of psychopathology. This focus is not meant to denigrate quantitative genetic research, which is even more valuable in the postgenomic era because it charts the course for molecular genetic research (Plomin et al. 2003a), nor is it meant to disparage research on environmental influences, which are as important as genetic influences for most types of psychopathology. For example, an exciting area of research on psychopathology is the developmental interactions and correlations between nature and nurture. Our focus on attempts to identify genes responsible for the heritability of psychopathology in the human species complements the previous *Annual Review of Psychology* chapter on behavioral genetics, which considered single-gene influences on brain and behavior primarily in nonhuman species (Wahlsten 1999), and a recent chapter on human quantitative genetic research on gene-environment interplay (Rutter & Silberg 2002).

THE HUMAN GENOME PROJECT

The twentieth century began with the rediscovery of Mendel's laws of heredity, which had been ignored by mainstream biologists for over 30 years. The word gene was first coined in 1903. Fifty years later the double helix structure of DNA was discovered. The genetic code was cracked in 1966. The crowning glory of genetics in the twentieth century was the culmination of the Human Genome Project, which provided a working draft of the sequence of all 3 billion letters of DNA in the human genome (International Human Genome Sequencing Consortium 2001).

For psychopathology the most important next step is the identification of the DNA sequences that make us different from each other. There is no single human genome sequence—we each have a unique genome. The vast majority of the DNA letters are the same for all human genomes, and many of these are the

same for other primates, other mammals, and even insects. Nevertheless, about one in every thousand nucleotide bases of DNA letters differs among people with at least 1% frequency, which means there are at least 3 million DNA variations. Although there are many types of these DNA differences, most involve a substitution of a single nucleotide base pair, called single nucleotide polymorphisms. DNA differences in the coding regions of genes or in the regions that regulate gene expression are responsible for the widespread heritability of psychopathology. That is, when we say that psychopathology is heritable, we mean that variations in DNA exist that increase (or decrease) risk of psychopathology. When all DNA variations are known, especially functional DNA variations that affect transcription and translation of DNA into proteins, the major beneficiary will be research on complex traits such as psychopathology that are influenced by multiple genes.

Progress is being made toward identifying all of the genes in the genome, but much remains to be learned—even about what a gene is. In the traditional sense of the "central dogma" of DNA, a gene is DNA that is transcribed into RNA and then translated into amino acid sequences. Less than 2% of the more than 3 billion bases of DNA in the human genome involves genes in which DNA is transcribed and translated in this way. It is not yet known how many such genes there are in the human genome. It used to be said that there are 100,000 genes, but the 2001 working draft of the human genome suggested far fewer, perhaps as few as 30,000, although estimates of the number of genes have been rising again as the genome becomes better understood. Moreover, some of the other 98% of DNA may be important, for example, DNA that is transcribed into RNA but not translated. For nearly all genes, a complicated process called splicing occurs between transcription and translation. All of the DNA within a gene is transcribed into RNA, but segments of RNA (called introns) are deleted and remain in the nucleus while the other segments (called exons) are spliced back together and exit the nucleus, where they are translated into amino acid sequences. Although in the past introns were thought to be genetic junk that has hitched a ride evolutionarily, it is now known that in some cases introns regulate the transcription of other genes. A recent finding is that many noncoding RNA sequences called microRNA act as genes by producing RNA molecules that regulate gene expression directly, rather than being translated into amino acid sequences (Eddy 2001). Exons are conserved evolutionarily—most of our exons are highly similar to DNA sequences in primates, mammals, and even invertebrates. This implies that the sheer number of such genes is not responsible for the greater complexity of the human species. Subtle variations in DNA rather than the number of genes are responsible for differences between mice and men (Brett et al. 2002). If subtle DNA differences are responsible for the differences between mice and men, even more subtle differences are likely to be responsible for individual differences within the human species. Although many rare and severe disorders caused by a single gene involve mutations in exons, DNA variations in introns and microRNA might be sources of more subtle effects on complex traits such as psychopathology.

THE POSTGENOMIC ERA

Functional Genomics and Behavioral Genomics

As advances from the Human Genome Project continue to be absorbed in DNA research on psychopathology, optimism is warranted about finding genes, the main topic of this review. The future of genetic research will involve a shift from finding genes to finding out how genes work, called functional genomics. Three huge areas of functional genomic research have emerged: gene manipulation, gene expression profiling, and proteomics (Phillips et al. 2002, Plomin & Crabbe 2000).

Gene Manipulation

One way to study how a gene works is to knock it out by breeding mice for which DNA sequences that prevent the gene from being transcribed have been deleted. These are called gene knock-out studies. Genes can also be inserted, or "knocked in." There has been an explosion of research using targeted mutations in mice (Phillips et al. 2002). Newer techniques can produce more subtle changes that alter the gene's regulation and lead to increases or decreases in the frequency with which the gene is transcribed. Techniques are even available to affect particular brain regions and to turn genes on and off at will. The approach is not without problems, however. Currently, there is no way to control the location of gene insertion in the mouse genome or the number of inserted copies of the gene, both of which can affect gene function.

A different approach, using antisense DNA, circumvents some of these problems and does not require breeding. Antisense DNA is a DNA sequence that binds to a specific RNA sequence and thus prevents some of the RNA from being translated, which "knocks down" gene function. Injected in the brain, antisense DNA has the advantage of high temporal and spatial resolution (Ogawa & Pfaff 1996). Antisense DNA knockdowns affect behavioral responses for dozens of drugs (Buck et al. 2000). The principal limitations of antisense technology currently are its unpredictable efficacy and a tendency to produce general toxicity.

Gene Expression Profiling

Genes are transcribed (expressed) as their products are needed. Gene expression can be indexed by the presence of messenger RNA (mRNA), which is transcribed from DNA and then travels outside the nucleus to form a template from which amino acids, the building blocks of proteins, are assembled in sequences in the process called translation. Microarrays are now available that can detect the expression of thousands of genes simultaneously. Unlike DNA studies, in which every cell in the body has the same DNA, gene expression studies depend on the tissue that is sampled. For psychopathology, brain is of course the critical tissue, which will make it difficult to apply this technology to humans. However, gene expression profiling is being used widely in research on animal models to compare brain tissue before and after an event in order to identify genes whose expression

is triggered by the event. For example, a gene expression profiling study of more than 7000 genes in 2 strains of mice investigated gene expression in the hippocampus during ethanol withdrawal following chronic ethanol exposure and found that about 100 genes are expressed in the hippocampus during withdrawal (Daniels & Buck 2002). Gene expression profiling is analogous to functional neuroimaging at the level of the gene.

Proteomics

Gene expression profiling assesses gene transcription as indexed by RNA. The next step toward functional genomics is to study the function of the proteins that result from translation of RNA. The term "protein genomics" led to the neologism "proteomics." Proteomics is much more difficult than genomics because, unlike the triplet code of DNA that governs the genome, there is no simple code for understanding the proteome. There are also several complications. First, it has been estimated that about half of all human genes are alternatively spliced into exons and introns and thus translated into different proteins (International Human Genome Sequencing Consortium 2001). Second, after translation proteins are also modified. It has been estimated that for each human gene three different modified proteins with different functions are produced (Banks et al. 2000). Third, although the amino acid sequence of a protein, its primary structure, can be predicted with certainty from the expressed DNA sequence, the mechanism determining secondary and tertiary folding upon which the properties of the protein depend, is currently poorly understood. Fourth, proteins tend to attach themselves to, or form complexes with, other proteins so that understanding protein function ultimately depends on the understanding of protein-protein interactions.

Behavioral Genomics

Gene manipulation, gene expression profiling, and proteomics are examples of bottom-up molecular biological approaches to functional genomics. Nearly all of this research is conducted using animal models because in humans it is not possible to manipulate genes and it is difficult to obtain brain tissue needed for gene expression profiling and proteomics. Although there are mouse models related to psychopathology [e.g., alcoholism (Crabbe 2003), anxiety (Lesch 2003), and dementia (Williams 2002a)], mouse models are obviously more problematic for cognitive disorders such as autism, reading disability, and communication disorders. Nonetheless, as genes are found, even for cognitive disorders, understanding how these genes work in the brain will profit from functional genomic research using animal models (Crusio & Gerlai 1999).

The bottom-up molecular biological approach to functional genomics is not the only level of analysis at which we can investigate how genes contribute to human psychopathology. At the other end of the continuum is a top-down level of analysis that considers the behavior of the whole organism. The term "behavioral genomics" has been suggested to emphasize the potential contribution of a top-down psychological level of analysis toward understanding how genes work

(Plomin & Crabbe 2000). For example, part of understanding how genes work is to understand how genetic effects interact and correlate with experience, how genetic effects on behavior contribute to change and continuity in development, and how genetic effects contribute to comorbidity and heterogeneity between disorders. These are issues central to quantitative genetic analysis, which has gone beyond merely estimating heritability (Plomin et al. 2002c). Behavioral genomic research using DNA will provide sharper scalpels to dissect these issues with greater precision (Plomin et al. 2002b).

Behavioral genomics will make important contributions toward understanding the functions of genes and will open up new horizons for understanding psychopathology. Few psychopathology researchers are likely to join the hunt for genes because it is difficult and expensive, but once genes are found it is relatively easy and inexpensive to make use of them. Although it used to be necessary to collect blood samples, DNA can now be obtained painlessly and inexpensively from cheek swabs. Cheek swabs yield enough DNA to genotype thousands of genes, and the cost of genotyping is surprisingly inexpensive. What has happened in the area of dementia in the elderly will be played out in many other areas of psychopathology. As discussed later, the only known risk factor for late-onset Alzheimer's dementia is the gene APOE. Although the association between APOE and LOAD was reported only a decade ago (Corder et al. 1993), it has already become routine in research on dementia to genotype subjects for APOE to ascertain whether the results differ for individuals with and without this genetic risk factor. For example, the association between APOE and dementia has been found to interact with head injury, smoking, cholesterol level, and estrogen level (Williams 2003). For these reasons, we predict that psychopathology researchers will routinely collect DNA in their research and incorporate identified gene associations in their analyses, which will greatly enrich behavioral genomics.

FINDING GENES

Greater progress by far has been made towards finding genes in the area of psychopathology than in any other area of psychology, although progress has nonetheless been slower than some had originally anticipated. We begin this review with the psychoses (schizophrenia and mood disorders) and then turn to cognitive disorders (dementia, autism, reading disability, communication disorders, mental retardation), and finally consider hyperactivity and alcoholism. Our goal is to provide overviews of recent linkages and associations in these areas, rather than to review quantitative genetic research, provide encyclopedic or historical reviews of molecular genetic research, or discuss the function of the genes (for more detail on these topics, see McGuffin et al. 2002, Plomin et al. 2003b).

A brief description of linkage and association may be useful (Bishop & Sham 2000, Sham 2003). Linkage is a departure from Mendel's law of independent assortment that posits that two genes will be inherited independently. Most of the

time independent assortment does take place, but Mendel did not know that genes are on chromosomes. If two DNA polymorphisms (sequences of DNA called DNA markers that differ between individuals)—for example, a DNA marker in a gene for a disorder and another DNA marker—are close together on a chromosome, they will tend to be inherited as a package within families rather than independently as predicted by Mendel. In this way, with a few hundred DNA markers, it is possible to screen the genome for cotransmission between a marker and a single-gene disorder within large family pedigrees. Linkage is most powerful for finding rare single-gene disorders in which a single gene is necessary and sufficient for the emergence of the disorder. For example, the linkage of Huntington's disease with DNA markers was found in a five-generation family of hundreds of individuals when a particular form (allele) of a DNA marker on chromosome 4 was only found in family members who had Huntington's disease (Gusella et al. 1983). Similar linkage studies have identified the chromosomal location of hundreds of single-gene disorders, and the precise DNA fault has been found for many of these disorders. Linkage only points to the neighborhood of a chromosome; a house-to-house search is then needed to find the culprit gene, a process that took 10 years in the case of Huntington's disease (Huntington Disease Collaborative Research Group 1993).

In the 1980s linkage studies of this type were also undertaken for psychopathology even though there was no evidence to suggest that such complex disorders are inherited as single-gene disorders. Early successes were claimed for bipolar depression (Egeland et al. 1987) and for schizophrenia (Sherrington et al. 1988), but neither claim was replicated. It is now clear that this traditional linkage approach can only detect a linkage if the gene has a large effect on the disorder, a situation best exemplified by relatively rare disorders such as Huntington's disease, which has a frequency of about 1 in 20,000 individuals. Common disorders such as psychopathology seldom show any sign of single-gene effects and appear to be caused by multiple genes as well as by multiple environmental factors. Indeed, quantitative genetic research suggests that such common disorders are usually the quantitative extreme of the same genes responsible for variation throughout the distribution (Plomin et al. 1994). Genes in such multiple-gene systems are called quantitative trait loci (QTLs) because they are likely to result in dimensions (quantitative continua) representing liability to disorders (qualitative dichotomies) that only manifest when a certain threshold is exceeded (Falconer 1965). The QTL perspective is the molecular genetic extension of quantitative genetics in which genetic variation tends to be quantitatively and normally distributed.

The goal of QTL research is not to find the gene for a complex trait but rather the multiple genes that make contributions of varying effect sizes to the variance of the trait. Perhaps one gene will be found that accounts for 5% of the trait variance, 5 other genes might each account for 2% of the variance, and 10 other genes might each account for 1% of the variance. If the effects of these QTLs are independent, they would in total account for 25% of the trait's variance. It is

unlikely that all of the genes that contribute to the heritability of a complex trait will be identified because some of their effects may be too small to detect or their effects may be nonadditive (called epistasis). The problem is that we do not know the distribution of effect sizes of QTLs for any complex trait in plant, animal, or human species. Not long ago a 10% effect size was thought to be small, at least from the single-gene perspective in which the effect size was essentially 100%. However, for behavioral disorders and dimensions, a 10% effect size may turn out to be a very large effect. If effect sizes are 1% or smaller, this would explain the slow progress to date in identifying genes associated with behavior because research so far has been woefully underpowered to detect and replicate QTLs of such small effect size (Cardon & Bell 2001). There can be no doubt that finding genes for complex disorders will be difficult (Sturt & McGuffin 1985, Weiss & Terwilliger 2000).

Recent research has been more successful in finding QTLs for complex traits because designs have been employed that can detect genes of much smaller effect size. Linkage has been extended to consider QTLs by using many small families (usually pairs of siblings) rather than a few large families. These QTL linkage methods can be used to study the extremes of a quantitative trait or a diagnosed disorder and are able to detect genes that account for about 10% of the variance of the quantitative trait or the assumed liability or susceptibility to the disorder with reasonable sample sizes. The essence of the most popular method, called sib-pair QTL linkage analysis, is to ask whether sharing alleles for a particular DNA marker makes siblings more similar phenotypically. Siblings can share none, one, or two of the alleles they inherit from their parents. Thus, in relation to a particular DNA marker, a pair of siblings can be like adoptive siblings sharing no alleles on average, like dizygotic twins sharing one allele on average, or like monozygotic twins sharing the same two alleles.

Sib-pair QTL linkage analysis assesses the extent to which allele sharing is correlated with sibling phenotypic resemblance. The most popular variant is called the affected sib-pair design, in which both siblings are diagnosed for a disorder (or both are extreme on a quantitative trait). Because the expectation is that siblings share one of their two alleles, linkage for the disorder is indicated if allele sharing is significantly greater than 50% when both siblings are affected.

The second method, called association (or linkage disequilibrium), can detect QTLs that account for much smaller amounts of variance than linkage (Edwards 1965, Risch 2000, Tabor et al. 2002). The fundamental reason for the greater power of association over linkage is that the information content for association is proportional to the QTL heritability (the effect size of the QTL), so that halving the effect size will increase the required sample size fourfold. In contrast, for linkage the information content is proportional to the square of the QTL heritability, so that halving the effect size will increase the required sample size 16-fold (Sham et al. 2000). Association is the correlation between a particular allele and a trait in the population. For example, as discussed below, a gene called apolipoprotein E (APOE) has an allele (called APOE-4), which has a frequency of about 40%

in individuals with late-onset Alzheimer's disease and about 15% in controls. APOE-4 has a large effect, but it is not necessary or sufficient for the development of the disorder—it is a risk factor that increases susceptibility to the disorder. At least a third of individuals with Alzheimer's disease lack the allele, and about half of individuals who have a double dose of this allele survive to age 80 without developing the disease (Williams 2003). It sounds contradictory to refer to a QTL association with a dichotomous disorder such as Alzheimer's disease because diagnosed disorders are present or absent rather than quantitative traits. However, if several genes contribute to the disorder, the genes will produce a continuum of liability to the disorder; only those whose liability exceeds a certain threshold will present as affected.

Most association studies involve case-control comparisons for diagnosed disorders or for extremes of a dimension. One problem with any comparison between two groups such as cases and controls is that inadequate matching between the two groups could jeopardize the conclusion that a particular QTL causes differences in psychopathology between the groups. A check on this possibility is to study associations within families, which controls for demographic differences between cases and controls (Abecasis et al. 2000, Spielman & Ewens 1996). Although such within-family designs have been favored in recent years, there is a strong tendency to use the more powerful and efficient case-control design to find associations and then to use within-family designs and other strategies (Pritchard & Rosenberg 1999) to confirm that associations are not spurious (Cardon 2003, Cardon & Bell 2001).

The following sections review recent linkage and association research on the most active areas of research in psychopathology: schizophrenia, mood disorders, dementia, autism, reading disability, communication disorders, mental retardation, hyperactivity, and alcoholism.

Schizophrenia

Despite large collaborative linkage studies carried out in Europe and North America, identification of the genes involved in schizophrenia remains elusive. Linkages that have received support from international collaborative studies include chromosome 6 (6p24-22), chromosome 8 (8p22-21), and chromosome 22 (22q11-12) (Owen & O'Donovan 2003). Other nominated linkages that have received some replication include chromosomes 1 (1q21-22), 5 (5q21-q31), 10 (10p15-p11), and 13 (13q14.1-q32) (Waterworth et al. 2002). However, in every case there are negative as well as positive findings. For example, a multicenter linkage study of 779 schizophrenic pedigrees excluded linkage on 1q (Levinson et al. 2002). The largest single-center systematic search for linkage, which included 196 affected sib pairs, effectively excluded any gene conferring a relative risk of 3 or more from over 80% of the genome (Williams et al. 1999). In order to detect linkages involving relative risks of 2 with a p of only .05, sample sizes of 800 affected sibling pairs will be needed (Scott et al. 1997).

Interestingly, the linkages on chromosomes 13 and 22 have also been reported to be linked with bipolar disorder (Berrettini 2000). This would be in keeping with the most recent analysis of twin data on schizophrenia and bipolar disorder, which suggests there is considerable genetic overlap (Cardno et al. 2002).

The focus on schizophrenia has turned to association studies that are capable of detecting genes with smaller effect sizes. The most obvious place to begin such studies is with candidate genes involved in the drugs that control schizophrenic symptoms, dopamine and serotonin receptors, although candidate gene studies are also being extended to other gene systems, with hundreds of such reports in recent years (Owen & O'Donovan 2003). Several studies have investigated common polymorphisms in a serotonin receptor gene (5HT2a). A meta-analysis based on more than 3000 subjects supports a small (odds ratios of 1.2 in which 1.0 represents chance) but significant role for the T102C polymorphism of 5HT2a (Williams et al. 1997). Sample sizes of 1000 cases and 1000 controls are required for 80% power to detect an effect of this size ($p < 0.05$). Interest in the dopamine D2 receptor gene faded after initial positive reports were countered by several negative reports from large studies (Owen & O'Donovan 2003). However, the gene that codes for the dopamine D3 receptor has yielded a significant odds ratio of 1.2 in a meta-analysis, although several negative results have been reported (Williams et al. 1998).

Mood Disorders

The story for major depression and bipolar depression is similar to schizophrenia. Large-scale linkage studies of bipolar depression have suggested linkages on chromosomes 12 (12q23-q24) and 21 (21q22) in several but not all studies (Badner & Gershon 2002, Baron 2002, Jones et al. 2002, Kalidindi & McGuffin 2003). Chromosome 18 linkage has also been suggested in several studies but the "hits" have not centered on a single region (Van Broeckhoven & Verheyen 1999). As mentioned in relation to schizophrenia, linkage has also been suggested on chromosomes 13 and 22 (Berrettini 2000). Several other linkage regions have been proposed in at least two studies such as chromosomes 1 (*1q31-32*) and 4 (*4p16*) (Baron 2002) and chromosomes 15 (*15q11*-q13) and 16 (*16p13*) (Kalidindi & McGuffin 2003). For unipolar depression, linkage studies have just begun and findings are unclear (Malhi et al. 2000).

As with schizophrenia, numerous recent studies of mood disorders have attempted to find associations with candidate genes. The gene that codes for serotonin transporter (hSERT) has received the most attention because it is involved in the reuptake of serotonin at brain synapses, which is the target for selective serotonin reuptake inhibitor antidepressants such as Prozac (fluoxetine). A functional repeat polymorphism in the hSERT promoter region (5HTTLPR) was reported to be associated with major depression in a study of 275 cases and 739 controls and with bipolar disorder in a study of 304 bipolar cases and 570 controls (Collier et al. 1996). However, in 8 follow-up studies totaling 719 cases of major depression

and 1195 controls, only one study replicated the original finding. For bipolar disorder, of 9 follow-up studies totaling 943 cases and 1164 controls, only two studies replicated the original finding (Lesch 2003). Beginning with a study in 1996 (Lesch et al. 1996), several studies have reported that 5HTTLPR is associated with anxiety-related dimensions in community samples, but 22 studies of more than 5000 subjects do not provide much support for this hypothesis (Lesch 2003). Stronger support for the involvement of 5HTTLPR comes from 8 studies of violent suicidal behavior, of which 5 are positive, and from 8 studies showing an effect on treatment response to selective 5HT transporter inhibitors, of which 6 are positive (Lesch 2003). One study has recently shown an association between 5HTTLPR and postpartum depression (Coyle et al. 2000).

Candidate genes in dopaminergic, noradrenergic, glutaminergic, and GABAergic pathways have also been investigated, but no clear associations have as yet emerged (Jones et al. 2002, Kalidindi & McGuffin 2003). For example, early association research focused on tyrosine hydroxylase, but a meta-analysis of 547 bipolar cases and 522 controls showed no significant effect (Turecki et al. 1997). Three association studies indicate that catechol-o-methyltransferase is associated with rapid cycling in bipolar disorder (Jones et al. 2002).

Candidate gene association studies have also begun to aim at other mood-related disorders such as anxiety and eating disorders, but no promising associations have as yet emerged (Eley et al. 2002). For example, a polymorphism in the promotor region of a serotonin receptor gene (5HT2A) was reported to be related to anorexia nervosa (Collier et al. 1997), but a subsequent meta-analysis showed no statistically significant association (Ziegler et al. 1999).

Dementia

Dementia yielded the first solid QTL finding and it remains the best success story. Research a decade ago focused on a rare (1 in 10,000) type of Alzheimer's disease that appears before 65 years of age and shows autosomal-dominant inheritance. Most of these early-onset cases are due to a gene (presenilin-1) on chromosome 14 (St. George-Hyslop et al. 1992) that was identified in 1995 (Sherrington et al. 1995). As is often the case with single-gene disorders, dozens of different mutations in presenilin-1 have been found, which will make screening difficult (Cruts et al. 1998). A similar gene, presenilin-2, on chromosome 1 and mutations in the amyloid precursor protein gene on chromosome 21 also account for a few early-onset cases (Liddell et al. 2002, Williams 2003).

The three genes that contribute to early onset Alzheimer's disease account for less than 2% of all Alzheimer's cases (Farrer et al. 1997). The great majority of Alzheimer's cases occur after 65 years of age, typically in people in their seventies and eighties. A major advance toward understanding late-onset Alzheimer's disease was the discovery of a strong allelic association with the apolipoprotein E gene (APOE) on chromosome 19 (Corder et al. 1993), the first QTL for psychopathology. This gene has three alleles (confusingly called alleles 2, 3, and 4).

The frequency of allele 4 is about 40% in individuals with Alzheimer's disease and 15% in control samples. This result translates to about a sixfold increased risk for late-onset Alzheimer's disease for individuals who have one or two of these alleles. In a meta-analysis of 40 studies involving 15,000 individuals, elevated frequencies of APOE-4 were found for Alzheimer's patients in each study, although the association was stronger among Caucasians and Japanese and weaker in African-Americans (Farrer et al. 1997). There is some evidence that allele 2, the least common allele, may play a protective role (Corder et al. 1994). Finding QTLs that protect rather than increase risk for a disorder is an important direction for genetic research on psychopathology.

APOE is a QTL in the sense that allele 4, although a risk factor, is neither necessary nor sufficient for developing dementia. For instance, at least a third of late-onset Alzheimer's patients do not have allele 4, and about half of individuals who have a double dose of this allele survive to age 80 without developing the disease (Williams 2003). Because APOE does not account for all the genetic influence on Alzheimer's disease, the search is on for other QTLs. New linkage studies of late-onset Alzheimer's have reported significant linkages on chromosomes 9 and 10 (Liddell et al. 2002, Williams 2003). Finally, more than 40 genes have shown some evidence of association with Alzheimer's disease, but none can be considered confirmed (Schellenberg et al. 2000).

Autism

Just 25 years ago, the origins of autism were thought by many to be entirely environmental, but family and twin studies altered this view, and autism is now one of the major targets for molecular genetic research. In 1998 an international collaborative linkage study reported a strong linkage on chromosome 7 (7q31-33) (International Molecular Genetic Study of Autism Consortium 1998). There have now been seven genome screens for linkage, six of which have found evidence for linkage in the 7q31-33 region (Pericak-Vance 2003). The specific gene in this region has not yet been identified (Bonora et al. 2002). Six of the seven genome screens have also found evidence for linkage on the short arm of chromosome 2, but the specific region differs across the studies. Other linkages have been reported in at least three studies on chromosomes 3, 13, 18, and 19 (Pericak-Vance 2003). A few candidate gene studies have been reported with particular attention on the serotonin transporter gene (Kim et al. 2002) and on genes in linkage regions (Folstein & Rosen-Sheidley 2001).

Reading Disability

One of the first QTLs found to be linked to a human behavioral disorder was a susceptibility gene for reading disability on chromosome 6 (6p21) (Cardon et al. 1994), a finding that has been replicated in three independent linkage studies (Willcutt et al. 2003). The 6p21 linkage has been found for diverse reading measures and also appears to be involved in hyperactivity (Willcutt et al. 2003).

Linkage has also been reported to chromosome 15 (15q21) in three studies (Williams 2002). Association studies are beginning to narrow down the regions on chromosomes 6 and 15 (Morris et al. 2000, Turic et al. 2002). The first genome screen for reading disability found linkage to chromosome 18 (18p11.2) in three samples (Fisher et al. 2002) and also replicated reports of linkage on chromosome 2 (Fagerheim et al. 1999, Petryshen et al. 2000). The linkages appear to be general to reading disability, including diverse processes such as single word reading, phonological and orthographic processing, and phoneme awareness (Fisher et al. 2002). When the specific genes are identified for these linkages, it will be interesting to investigate the extent to which the genes' effects are specific to reading or extend more broadly to language and other cognitive processes (Fisher & Smith 2001).

Communication Disorders

Although molecular genetics has only recently come to communication disorders, several successes have been reported (Fisher 2003). The first gene identified for language impairment involves a unique type of language impairment in a single family known as the KE family. This much-studied family includes 15 linguistically impaired relatives whose speech has low intelligibility and whose deficits involve nearly all aspects of language. In this three-generation family, transmission of the disorder was consistent with a single-gene autosomal dominant pattern of inheritance. A linkage region (SPCH1) was identified on the long arm of chromosome 7 (7q31) (Fisher et al. 1998). The linkage has recently been shown to be due to a single nucleotide substitution in the exon 14 coding region of a gene (FOXP2) in the forkhead/winged-helix (FOX) family of transcription factors (Lai et al. 2001). Despite the authors' caution in noting that the KE family's unusual type of speech and language impairment with a single-gene autosomal inheritance pattern has not been found in any other family, the FOXP2 finding has been hailed in the media as "the language gene." However, a study of 270 low-language children screened from more than 18,000 children showed that not a single child had the FOXP2 mutation (Meaburn et al. 2002). In other words, although the exon 14 FOXP2 mutation appears to be responsible for the unusual speech and language disorder of the KE family, the mutation is not found among children with common language impairment. Other coding-region variants in the FOXP2 gene also show no association with common forms of language impairment (Newbury et al. 2002).

The first genome-wide QTL linkage screen for language impairment has recently been reported (SLI Consortium 2002). The research was a sib-pair QTL linkage study of 252 children from 5 to 19 years old in 98 families in which at least one sibling met selection criteria (at least 1.5 standard deviations below the norms on either expressive or receptive language tests). In addition to expressive and receptive language, phonological short-term memory (nonword repetition) was also assessed. The children were genotyped for 400 markers evenly distributed

throughout the genome. The results for all possible sibling pairings suggested linkage on 16q for the nonword repetition test and on 19q for the test of expressive language. Because linkage designs, even QTL linkage designs, can only detect relatively large effects on the order of 10% heritabilities or greater, these findings suggest two genes of large effect, each of which is specific to a single language measure.

Although a QTL linkage of this magnitude has been found for reading disability, a QTL perspective would expect that most genes show a smaller effect size. Moreover, quantitative genetic research suggests that genetic effects on language impairment are general rather than specific to one language process (Dale et al. 2000). Another molecular genetic study of language disability is underway that incorporates several recent trends in QTL research with the goal of identifying language-general QTLs of small effect size (Plomin et al. 2002a). Language-impaired children were identified, not from diagnoses, but from the extreme of a general language factor that emerged from factor analyses of nine diverse tests of language (Colledge et al. 2002). Because large samples and association designs are needed to detect QTLs of small effect size, the study includes 300 language-impaired children and 1000 control subjects in a case-control association design. The design uses a direct association approach in which DNA markers are assessed that can be presumed to be QTLs themselves rather than the much less powerful indirect association approach that uses anonymous DNA markers indirectly associated with the QTL, which is in turn directly associated with the trait. Also, rather than investigating the few available functional DNA markers in candidate genes, a systematic genome scan is being conducted of all DNA markers in coding regions of genes that result in an amino acid substitution. Although such DNA markers are not necessarily functional they are much more likely to be functional than the millions of DNA markers in noncoding regions. Genotyping thousands of DNA markers for such large samples would be daunting, but a technique called DNA pooling is used in which DNA is pooled from the language-impaired group and from the control group (Daniels et al. 1998). The two pools of DNA are genotyped rather than the DNA of all of the individuals in the groups. In order to avoid false positive results, the study includes various replications such as a within-family analysis based on dizygotic twin pairs, which controls for ethnic stratification. This general strategy has been used in the first genome scan for QTL association for cognitive ability (Plomin et al. 2001b), but results have not as yet been reported for the association genome scan of language disability.

Mental Retardation

More than 200 genetic disorders, most extremely rare, include mental retardation among their symptoms (Zechner et al. 2001). For example, phenylketonuria is a single-gene recessive disorder that occurs in about 1 in 10,000 births. Like many other single-gene disorders, the molecular genetics of phenylketonuria is not simple. More than 100 different mutations, some of which cause milder forms

of retardation, have been found in the gene (PAH) on chromosome 12 that produces the enzyme phenylalanine hydroxylase (Guldberg et al. 1998).

An important genetic discovery about two decades ago was the association with mental retardation of apparent microscopic breakages, "fragile sites," on the X chromosome. Fragile X syndrome is now known to be the second most common specific cause of mental retardation after Down syndrome (Kaufmann & Reiss 1999). Until the gene for fragile X was identified in 1991, its inheritance was puzzling because its risk increased across generations (Verkerk et al. 1991). The fragile X syndrome is caused by an expanded triplet repeat (CGG) on the X chromosome (Xq27.3). Parents who inherit X chromosomes with a normal number of repeats (6–54) can produce eggs or sperm with an expanded number of repeats (up to 200), called a premutation. This premutation does not cause retardation in their offspring, but it is unstable and often leads to much greater expansions in later generations, especially when it is inherited through the mother. The risk that a premutation will expand to a full mutation increases over four generations from 5 to 50%, although it is not yet possible to predict when a premutation will expand to a full mutation. The full mutation causes fragile X in almost all males but in only half of the females who are mosaics for the X chromosome in the sense that one X chromosome is inactivated. The triplet repeat is adjacent to a gene (FMR1), and a full mutation prevents that gene from being transcribed. Its protein product (FMRP) appears to bind RNA, which means the gene product regulates expression of other genes (Weiler et al. 1997).

Three of the most common single-gene disorders that show effects on IQ but whose primary problem is something other than retardation are Duchenne muscular dystrophy, Lesch-Nyhan syndrome, and neurofibromatosis, caused by genes on Xp21, Xq26, and 17q11.2, respectively. Much more common than such single-gene causes of mental retardation are chromosomal abnormalities that lead to mental retardation. Most common are abnormalities that involve an entire extra chromosome, such as Down syndrome, caused by a trisomy of chromosome 21, which is the single most prevalent cause of mental retardation, occurring in 1 in 1000 births. As the resolution of chromosomal analysis becomes finer, more minor deletions are being found. A study of children with unexplained moderate to severe retardation found that 7% percent of them had subtle chromosomal abnormalities as compared with only 0.5% of children with mild retardation (Knight et al. 1999).

Although severe mental retardation has drastic consequences for the affected individual, mild mental retardation has a larger cumulative effect on society because many more individuals are affected. Despite its importance, there has never been a major twin or adoption study of mild mental retardation, and perhaps as a result there have been no QTL studies. Rather than assuming that mild mental retardation is due to a concatenation of rare single-gene or chromosomal causes, the QTL hypothesis is that mild mental retardation is caused by the same multiple genes that operate throughout the distribution to affect cognitive ability (Plomin 1999).

Hyperactivity

Recent twin study evidence for high heritability of attention-deficit hyperactivity disorder as well as a continuous dimension of hyperactive symptoms has led to a surge in molecular genetic research (Thapar et al. 1999). Although sib-pair linkage studies are underway, most of this research has concentrated on candidate gene association studies. Several groups have reported evidence of associations with the dopamine D4 receptor gene (DRD4), the dopamine transporter gene (DAT1), and the dopamine D5 receptor gene (DRD5) (Thapar 2003). For DRD4, 11 of 15 published studies have found evidence of association comparing cases and controls, and a meta-analysis indicates a significant effect with an odds ratio of ~2 (Faraone et al. 2001). Two of three studies have found a stronger DRD4 association for children who respond well to methylphenidate (Thapar 2003). Meta-analysis of published results for DAT1 found six studies showing significant association and four that did not, with an overall odds ratio of 1.16 (Curran et al. 2001). However, there was significant evidence of heterogeneity between the datasets, and recently a far greater odds ratio of 8 has been reported in a Taiwanese population (Chen et al. 2002). A recent study of 311 pairs of unselected dizygotic twins found significant association between DAT1 and hyperactivity as a quantitative trait both within and between twin pairs (Asherson et al. 2002). DRD5 was also associated with hyperactivity (Daly et al. 1999), and three independent studies have subsequently shown nonsignificant trends in the same direction (Thapar 2003). Finally, two recent reports found evidence for association between a single nucleotide polymorphism in the 5HT1B gene in two large collaborative datasets (Hawi et al. 2002, Quist et al. 2002).

Alcoholism

The most well-known association with alcoholism is a recessive allele (ALDH2*2) that leads to low activity of acetaldehyde dehydrogenase, a key enzyme in the metabolism of alcohol. The buildup of acetaldehyde after alcohol is consumed leads to unpleasant symptoms such as flushing and nausea, thus protecting individuals against development of alcoholism. About half of East Asian individuals are homozygous for ALDH2*2, and hardly any such individuals have been found to be alcoholic. This is the major reason why rates of alcoholism are much lower in Asian than in Caucasian populations (Heath et al. 2003). Moreover, in a Japanese population, individuals with two copies of the ALDH2*2 allele consume ten times less alcohol per month than individuals who do not have the ALDH2*2 allele. Individuals with just one copy of the ALDH2*2 allele drink three times less per month than individuals without the allele (Higuchi et al. 1994). However, because the ALDH2*2 allele is rare in European populations, it contributes only negligibly to alcoholism in European populations (Borras et al. 2000).

Many early studies focused on a common polymorphism close to the dopamine D2 receptor, an association first reported in 1990 (Blum et al. 1990), which led to media reports that "the alcoholism gene" had been found. Subsequent failures to

reproduce these results led to an equally uninformed backlash that damaged the credibility of association mapping efforts for all complex traits. A decade later the association remains controversial (Gorwood et al. 2000). A special issue for this dopamine D2 receptor gene polymorphism is that it shows large frequency differences between populations, as does alcoholism, which could create spurious associations if probands and controls are not well matched (Gelernter et al. 1993). Supporting this concern are the negative results that have come from research using within-family designs that control for ethnic stratification (Edenberg et al. 1998).

Of all of the candidate genes examined for association with alcoholism, the most promising are $GABA_A$ receptor genes (on chromosome 5q33-34). Several linkage studies of alcoholism have also been reported (Reich et al. 1999). A large QTL linkage study called the Collaborative Study on the Genetics of Alcoholism (COGA) includes 105 multigenerational families and 1200 families with at least three first-degree relatives including the alcoholic proband (Reich et al. 1998). For the multigenerational families, linkage was suggested on chromosomes 1, 4, and 7. COGA collaborations have led to publication of 68 papers describing diverse analyses of this remarkable dataset (Almasy & Borecki 1999). QTL research has begun to turn to other drugs of abuse, but no clear associations have yet emerged (Ball & Collier 2002, Heath et al. 2003). A promising new area for QTL research is individual differences in response to psychotropic medication (Aitchison & Gill 2003, Masellis et al. 2002).

Although mouse models have been developed for several domains such as depression, anxiety, dementia, and hyperactivity, they have been most widely used for finding QTLs in psychopharmacogenetics, especially for alcohol-related behavior (Craig & McClay 2003). Association studies of mice have definitively mapped at least 24 QTLs for alcohol drinking, alcohol-induced loss of righting reflex, and acute alcohol withdrawal, as well as other drug responses (Crabbe et al. 1999). Current research aims to narrow the chromosomal address of these QTL regions (e.g., Fehr et al. 2002). One study identified 5 QTLs that are associated with the large difference between lines selected for alcohol sensitivity (Markel et al. 1997). Alcohol sensitivity was assessed by sedation or "sleep time" following a dose of alcohol, with the "long-sleep" and "short-sleep" lines differing by 170 minutes. Each of the 5 QTLs conferred a difference in sleep time of about 20 minutes. Thus, if a mouse possessed all 5 short-sleep alleles, its genotype could account for 130 minutes of the total of 170 minutes in sleep-time difference between the long-sleep and short-sleep mice. Finding such sets of QTLs is the goal for human psychopathology. Despite the ability of mouse models to identify QTLs, mouse model QTL research on alcohol has not yet led to the identification of QTLs for human alcoholism. As noted earlier, mouse models are likely to be of greatest benefit for understanding how genes work (functional genomics) rather than for finding human QTLs. The special power of mouse models is the ability to control and manipulate both genotype and environment (Crabbe 2003, Phillips et al. 2002).

CONCLUSIONS

Early molecular genetic work focused on single-gene disorders in which a single gene is necessary and sufficient for a disorder. However, single-gene disorders tend to be severe but rare, whereas less severe but common disorders typical of psychopathology are likely to be influenced by multiple genes. The most recent example is the finding that a mutation in the FOXP2 gene causes language impairment of a severe and unusual sort (Lai et al. 2001). This mutation appears to be unique to the KE family; for example, the mutation was not found in a single child in a sample of 270 low-language children (Meaburn et al. 2002). Similarly, rare single-gene disorders have been found for early-onset dementia and severe mental retardation. It is possible, but seems highly unlikely, that common disorders are a concatenation of such rare single-gene disorders, a hypothesis facetiously called the one-gene-one-disorder (OGOD) hypothesis (Plomin et al. 1994). The field has moved toward a QTL hypothesis, which assumes that multiple genes affect common disorders and result in a quantitative continuum of vulnerability. This QTL perspective suggests that common disorders are the quantitative extreme of the same genetic factors responsible for variation throughout the distribution. The QTL hypothesis is by no means proven, but it is entirely an empirical issue. It predicts that when genes are found that are associated with common psychopathology the genes will be associated with variation throughout the distribution. Thus, phenotypic measurement (Farmer et al. 2002) will continue to be a key issue, but diagnosis of a precise cut-off for psychopathology will be of less concern because cut-offs are arbitrary if disorders are really the extremes of dimensions. For example, a recent book on molecular genetic research on personality views personality traits as endophenotypes of psychiatric disorders (Benjamin et al. 2002).

A major implication of this QTL perspective is that if multiple genes affect common disorders typical of psychopathology, the effect size of a particular gene is likely to be small. However, the distribution of effect sizes of QTLs is not known for any complex trait. From the single-gene perspective, in which the effect size of a gene is 100%, an effect size of 10% seems small. An effect size of 10% is in the range that can be detected by QTL linkage designs with feasible sample sizes. QTL linkages as in the case of the 6p21 linkage for reading disability and the APOE association with late-onset Alzheimer's disease indicate that there are some QTLs of this magnitude. However, the slow progress in identifying replicable associations for complex traits seems most likely to be due to a lack of power to detect QTLs of much smaller effect size (Cardon & Bell 2001). For this reason, it has been recommended that QTL studies aim to break the 1% barrier (Plomin et al. 2003b). Breaking this QTL barrier will require direct association designs using functional polymorphisms and sample sizes much larger than we have seen so far. A gloomier prospect is that if QTL effect sizes are less than 1% or if QTLs interact, it will be difficult to detect them reliably. If that is the case, the solution is to increase the power of research designs even more in order to track down the QTLs responsible for the ubiquitous and substantial heritability of psychopathology. DNA pooling,

mentioned above, will be useful in this context because it costs no more to genotype 1000 individuals than 100 individuals.

Although molecular genetic research in psychopathology only began in earnest a decade ago, this is an extremely energetic and exciting area of research. Its future looks bright because complex traits like psychopathology will be the major beneficiaries of postgenomic developments that facilitate the investigation of complex traits influenced by many genes as well as by many environmental factors. This will happen first by finding genes associated with psychopathology and then by understanding the mechanisms by which those genes affect psychopathology at all levels of analysis from the cell to the brain to the whole organism. The most exciting prospect is the integration of quantitative genetics, molecular genetics, and functional genomics for a new focus on behavioral genomics. This integration is more than methodological and technological. Because DNA is the ultimate common denominator, genetic research on psychopathology in the postgenomic era will become increasingly integrated into the life sciences.

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